Ketrol

30mg/ml
IV/IM Injection

(Ketorolac Tromethamine)

کیٹرول

۳۰ ملی گرام/ملی لیٹر
وریدی/عضلاتی انجکشن

(کیٹورولیک ٹرومیتھامین)

COMPOSITION:
Each 1ml ampoule contains:
Ketorolac tromethamine.....30mg
(USP Specifications)

DESCRIPTION:
Ketorolac tromethamine, a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term (up to 5 days) management of moderately severe, acute pain, that requires analgesia at the opioid level. **KETROL** is a potent analgesic agent of the non-steroidal, anti-inflammatory class (NSAID). Its mode of action is to inhibit the cyclo-oxygenase enzyme system and hence prostaglandin synthesis and it demonstrates a minimal anti-inflammatory effect at its analgesic dose.

MECHANISM OF ACTION:
The primary mechanism of action responsible for ketorolac's anti-inflammatory, antipyretic and analgesic effects is the inhibition of prostaglandin synthesis by competitive blocking of the enzyme cyclooxygenase (COX). Ketorolac is a non-selective COX inhibitor.

INDICATIONS:
Ketorolac is indicated for short-term management of moderate to severe pain.Concerns about the high incidence of reported side effects led to restriction in its dosage and maximum duration of use. In the UK, treatment should be initiated only in a hospital. Maximum duration of treatment should not exceed five days for tablets (per package insert), or two days for continuous daily dosing with intravenous or intramuscular formulations. The ophthalmic formulation can be used instead of steroidal anti-inflammatories in cases where a raised intraocular pressure (glaucoma) is to be avoided.

DOSAGE & ADMINISTRATION:
KETROL ampoules are for administration by intramuscular or bolus intravenous injection. Bolus intravenous doses should be given over no less than 15 secs. **KETROL** ampoules should not be used for epidural or spinal administration. The time to onset of analgesic effect following both i.v & i.m administration is similar is approximately 30minutes with maximum analgesia occurring within 1-2 hrs. The median duration of analgesia is generally 4-6 hrs. Dosage should be adjusted according to severity of the pain. Dosage should be adjusted according to the severity of pain and the patient response.

Duration of treatment:
The administration of continuous multiple daily doses of KETROL intramuscularly or intravenously should not exceed 2 days because adverse events may increase with prolonged usage. There has been limited experience with dosing for longer periods since the vast majority of patients have transferred to oral medication or no longer require analgesic therapy after this time

Adults
Recommended initial dose of **KETROL** 10mg, followed by 10-30mg every 4-6 hrs. as required. In the initial post-operative period, **KETROL** may be given as often as every 2 hours if needed. The lowest effective dose should be given. A total daily dose of 90 mg for non- elderly and 60 mg for elderly, renally impaired patients and patients less than 50 kg should not be exceeded. The maximum duration of treatment should not exceed two days. For patient receiving **KETROL** ampoule and who are converted to **KETROL** tablets, total combined daily dose should not exceed 90mg (60mg for elderly renally impaired patients and patients less than 50 kg) and oral component should not exceed 40mg on the day the change of formulation is made. Patient converted to oral treatment as soon as possible.

SPECIAL DOSAGE INSTRUCTIONS:
- **Elderly patients:**

For patients over 65 years, lower end of dosage range is recommended. Total daily dose of 60mg should not be exceeded.

- **Children**

Safety & efficacy in children have not been established. Therefore, KETROL is contraindicated for use in children under 16 yrs. of age

- **Renal impairment**

Since Ketorolac tromethamine and its metabolites are excreted mainly by the kidney so it is contraindicated in moderate to severe renal impairment serum creatinine > 160 μmol / liter. Patients with lesser renal impairment should receive a reduced dose (not exceeding 60mg /day i.v or i.m.) and their renal status should be clearly monitored,

- **Combination treatment**

Opioid analgesics like morphine and pethidine may be used concomitantly and may be required for optimal analgesic effect in early post-operative period when pain is not severe. **KETROL** does not interfere with opioid binding and does not exacerbate opioid related respiratory depression or sedation. When used in combination with ketrol ampoules, daily dose of opioid is usually less than the normally required. However, side effects of opioid should still be considered especially in day case surgery.

PHARMACOKINETICS:
Following *intramuscular* administration, ketorolac tromethamine was rapidly and completely absorbed, a mean peak plasma concentration of 2.2 ug/ml occurring an average of 50 minutes after a single 30 mg dose. The influences of age, kidney and liver function on terminal plasma half-life and mean total, clearance are outlined in the table below (estimated from a single 30 mg I.M dose of ketorolac tromethamine).

Type of Patients	Total of clearance (1/h/kg) mean (range)	Terminal half-life (h) mean (range)
Normal Patients (n = 54)	0.023 (0.010-0.046)	5.3(3.5-9.2)
Patients with haptic impairment (n=7)	0.029 (0.013-0.066)	5.4 (2.2-6.9)
Patients with renal impairment (serum creatinine 160-430 umo/a) (n=25)	0.016 (0.003-0.043)	10.3(5.9-19.2)
Renal Dialysis patients (n=9)	0.016 (0.003-0.036)	13.6 (8.0-39.1)
Healthy elderly patients (mean age 72) (n=13)	0.019 (0.013-0.034)	7.0 (4.7-8.6)

Intravenous administration of a single 10 mg dose of ketorolac tromethamine resulted in a mean peak plasma concentration of 2.4 ug/ml occurring an average of 5.4 minutes after dosing, with an average terminal plasma elimination half-life of 5.1 hours, an average volume of distribution of 0.15 l/kg, and a total plasma clearance of 0.35 ml/min/kg.
The pharmacokinetics of ketorolac tromethamine in man following single *or* multiple doses are linear. Steady-state plasma levels are achieved after dosing every 6 hours for one day. No changes in clearance occur with continued dosing. The primary route of excretion of ketorolac tromethamine and its metabolites is renal: 91.4% (mean) of a given dose being found in the urine and 6.1% (mean) in the feces.
More than 99% of the ketorolac tromethamine in plasma is protein-bound over a wide concentration range.

PRECAUTIONS:
Physicians should be aware that in some patients pain relief may take longer than 30 minutes after i.v. or i.m. administration.

- **Elderly patients**:

Patients over the age of 65 years may be at a greater risk of experiencing undesirable effects than younger patients. This age-related risk is common to all NSAIDs. Compared to young adults, the elderly have an increased plasma half-life and reduced plasma clearance of ketorolac tromethamine. With **KETROL** ampoules, a total daily dose >60 mg is not recommended.

- **Gastrointestinal effects**:

KETROL can cause gastrointestinal irritation, ulcers or bleeding in patients with or without a history of previous symptoms. Elderly and debilitated patients are more prone to develop these reactions. The incidence increases with dose and duration of treatment. In a non-randomized, in-hospital post-marketing surveillance study, increased rates of clinically serious gastrointestinal bleeding were seen in patients <65 years of age who received an average daily dose of > 90 mg **KETROL** i.m. as compared to those patients receiving parenteral opioids.

- **Respiratory effects:**

Bronchospasm may be precipitated in patients with a history of asthma.

- **Renal effects:**

Drugs that inhibit prostaglandin biosynthesis (including NSAIDs)have been reported to cause nephrotoxicity, including but not limited to glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome and acute renal failure. In patients with renal, cardiac or hepatic impairment, caution is required since the use of NSAIDs may result in deterioration of renal function.
As with other drugs that inhibit prostaglandin synthesis,

elevations of serum urea, creatinine and potassium have been reported with **KETROL** and may occur after one dose.
Impaired renal function: Caution should be observed in patients with conditions leading to a reduction in blood volume and/or renal blood flow, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate overt renal failure. Patients at greatest risk of this reaction are those who are volume- depleted because of blood loss or severe dehydration, patients with impaired renal function, heart failure, liver impairment, the elderly and those taking diuretics. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state. Inadequate fluid/blood replacement during surgery, leading to hypovolemia, may lead to renal dysfunction which could be exacerbated when **KETROL** is administered. Therefore, volume depletion should be corrected and dose monitoring of serum urea and creatinine and urine output is recommended until the patient is normovolemic. In patients on renal dialysis, ketorolac tromethamine clearance was reduced to approximately half the normal rate and terminal half-life increased approximately three-fold.
•Fluid retention and edema: Fluid retention and edema have been reported with the use of **KETROL** and it should therefore be used with caution in patients with cardiac decompensation, hypertension or similar conditions.
• **Hepatic effects:**
Borderline elevations of one or more liver function tests may occur. These abnormalities may be transient, may remain unchanged, or oppress with continued therapy. Meaningful elevations (greater than ^THmes normal) of serum glutamate pyruvate transaminase e~(SGPT/ALT) or serum glutamate oxaloacetate transaminase (SGOT/AST) occurred in controlled clinical trials in less than 1% of patients/ If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, **KETROL** should be discontinued.
• **Hematological effects:**
Patients with coagulation disorders should not receive **KETROL**. Patients on anticoagulation therapy may be at increased risk of bleeding if given **KETROL** concurrently. The concomitant use of ketorolac tromethamine and prophylactic low-dose heparin (2,500-5,000 units 12-hourly) has not been studied extensively and may also be associated with an increased risk of bleeding. Patients already on anticoagulants or who require low-dose heparin should not receive ketorolac tromethamine. Patients who are receiving other drug therapy that interferes with homeostasis should be carefully observed. In controlled clinical studies, the incidence of clinically significant postoperative bleeding was less than 1%.
•Ketorolac tromethamine inhibits platelet aggregation and prolongs bleeding time. In patients with normal bleeding function, bleeding times were raised, but not outside the normal range of 2 to 11 minutes. Unlike the prolonged effects from aspirin, platelet function returns to normal within 24-48 hours after ketorolac tromethamine is discontinued.
• **Pregnancy, nursing mothers**
The safety of **KETROL** in human pregnancy has not been established. **KETROL** is therefore contraindicated during pregnancy, labored delivery, As ketorolac tromethamine has been detected in human milk at low levels, it is also contraindicated in mothers who are breast-feeding.

UNDESIRABLE EFFECTS:

• **Gastrointestinal tract:**
Abdominal discomfort, constipation, diarrhea, dyspepsia, eructation, flatulence, fullness, gastritis, gastrointestinal bleeding, gastrointestinal pain, nausea, pancreatitis, peptic ulcer, perforation, stomatitis, vomiting. Central nervous/ musculoskeletal systems: abnormal dreams, abnormal taste and vision, abnormal thinking, aseptic meningitis, convulsions, depression, dizziness, drowsiness, dry mouth, euphoria, excessive thirst, functional disorders, hallucinations, headache, hearing loss, hyperkinesia, inability to concentrate, insomnia, myalgia, nervousness, paresthesia, stimulation, sweating, tinnitus, vertigo.
• **Urinary tract and kidneys**:
Acute renal failure, flank pain (with or without hematuria), glomerular nephritis, hemolytic uremic syndrome, hyperkalemia, hyponatremia, increased urinary frequency, interstitial nephritis, nephrotic syndrome, oliguria, raised serum urea and creatinine, renal papillary necrosis. Cardiovascular/ hematological systems: bradycardia, flushing, hypertension, pallor, purpura thrombocytopenia.
• **Respiratory system:** asthma, dyspnea, pulmonary edema. Skin: exfoliative dermatitis, Lyell's syndrome, maculopapular rash, pruritus, Stevens-Johnson syndrome, urticaria.
• **Hypersensitivity reactions:** anaphylaxis, bronchospasm, flushing and rash, -hypotension, laryngeal edema. Such reactions may occur in patients with or without known sensitivity to **KETROL** or other NSAIDs.
• **Bleeding:** epistaxis, hematomata, postoperative wound hemorrhage. Other: abnormal liver function tests, asthenia, edema, injection site pain, weight gain.

DRUG INTERACTIONS:

Concurrent treatment with probenecid is contraindicated because of increases in ketorolac tromethamine plasma level and half-life.
Because of an increased tendency to bleeding when oxpentifylline is administered concurrently, this combination is contraindicated.
Concurrent treatment with lithium is contraindicated because there is a possible inhibition of renal lithium clearance, increased plasma lithium concentration, and potential lithium toxicity.
KETROL should not be used with other NSAIDs because of the potential for additive side effects, ketorolac tromethamine is highly bound to human plasma protein (>99%) and binding is concentration-independent. Because ketorolac tromethamine is a highly potent drug and present in low concentrations in plasma, it would not be, expected to displace other protein-bound drugs significantly.
ketorolac tromethamine did not alter digoxin protein binding, in-vitro studies indicated that at therapeutic concentrations and above of salicylate (>300 ng/ml), the binding of ketorolac tromethamine was reduced from approximately 99.2-97.5%. Therapeutic concentrations of digoxin, warfarin, paracetamol,
There is no evidence in animal or human studies that ketorolac tromethamine induces or inhibits the hepatic enzymes capable of metabolizing itself or other drugs. Hence KETROL would not be expected to alter the pharmacokinetics of other drugs due to enzyme induction or inhibition mechanisms.

OVERDOSAGE:

Doses of 360 mg given intramuscularly over an 8-hour interval for 5 consecutive days have caused abdominal pain and peptic ulcers which have healed after discontinuation of dosing. Two patients recovered from unsuccessful suicide attempts. One patient experienced nausea after 210 mg **KETROL**, and the other hyperventilation after 300 mg **KETROL**.

SPECIAL REMARKS:

• **Incompatibilities**
KETROL ampoules should not be mixed in a small volume (e.g. in a syringe) with morphine sulphate, pethidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride as precipitation of ketorolac tromethamine will occur.
KETROL ampoules are compatible with normal saline, 5% dextrose, Ringer's solution, Ringer- Lactate solution or Plasmalyte solution. Compatibility with other drugs is unknown.
• **Stability**
This medicine must not be used after the expiry date (EXP) shown on the pack **KETROL**. **KETROL** ampoules must not be used if particulate matter is present in the solution.

CONTRAINDICATIONS:

A history-of peptic ulcer or gastrointestinal bleeding suspected or confirmed cerebrovascular bleeding hemorrhagic diatheses, including coagulation disorders
patients with hypersensitivity to ketorolac tromethamine or other NSAIDs and patients in whom aspirin or other prostaglandin synthesis inhibitors induce allergic reactions (severe anaphylactic-like reactions have been observed in such patients)patients with the complete or partial syndrome of nasal polyps, angio- edema or bronchospasm concurrent treatment with other NSAIDs, oxpentifylline, probenecid or lithium salts hypovolemia from any cause, or dehydration moderate or severe renal impairment (serum creatinine >160jamol/l) a history of asthma patients who have had operations with a high risk of hemorrhage or incomplete homeostasi patients on anticoagulants including low-dose heparin (2500-5000 units 12-hourly) during pregnancy, labor, delivery or lactation children under 16 years of age.

STORAGE & INSTRUCTIONS:

Store between 15-25°C.
Protect from heat, sunlight & light.
Keep away from the reach of children.
To be sold on prescription of a registered medical practitioner only.

HOW SUPPLIED:

1ml x 5's Ampoules.

خوراک وطریقہ استعمال:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:
دوا کو ۱۵ - ۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان ٹھنڈی اور خشک جگہ پر رکھیں۔ دھوپ، گرمی اور روشنی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔ انجیکشن کے ایک ہونے، دھندلا ہونے یا اس میں ذرات نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔
صرف معتمد ڈاکٹر کے نسخے پر فروخت کریں۔

Manufactured by:
PHARMASOL
PRIVATE LIMITED
Plot # 549, Sundar Industrial Estate,
Lahore, Pakistan.